THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon

Serial No.: 08/823,999 Group Art Unit: 1644

Filed: March 25, 1997 Examiner: Phillip Gambel

For: *MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION*

Assistant Commissioner
of Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-12 in the Office Action mailed August 16, 1999 in the above-identified patent application. A Notice of Appeal was mailed on January 18, 2000. A Petition for an Extension of Time for three months, the appropriate fee of $435 for a three month extension of time for a small entity, and $150 for filing of Appellants' Brief, and a Proposed Amendment are also enclosed.

(1) REAL PARTY IN INTEREST

The real parties in interest of this application are Massachusetts Institute of Technology, Cambridge, MA and Brigham and Women's Hospital, Boston, MA.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-12 are pending. Claims 7 and 9 were withdrawn as directed to a non-elected invention. The Advisory Action mailed December 29, 1999, indicated that the Amendment dated November 19, 1999, would be entered and the Amendment dated December 3, 1999, would not be entered. The text of each claim on appeal, as amended, is set forth in Appendix I to this Appeal Brief. The text of each claim as proposed to be amended is set forth in Appendix II to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment dated November 15, 1999. An Amendment accompanies this Appeal Brief.

(5) SUMMARY OF THE INVENTION

The compositions described herein are used to inhibit undesired response to vascular injury that includes hyperplasia of vascular smooth muscle cells which occurs in response to injury of blood vessels, for example, as a result of angioplasty, atherectomy, endovascular

stenting coronary or peripheral arterial bypass used to open a stenotic or occluded vessel or transplantation of cells, tissue or organs. Vascular smooth muscle cell hyperplasia triggered by the injured vessel can result in stenosis or restenosis of the blood vessel. These compositions and methods are based on the discovery that inhibition of integrin-mediated leukocyte adhesion and/or function, especially adhesion and function of monocytes and granulocytes, can significantly reduce restenosis. (page 6, lines 12-23)

Restenosis is an extremely complex phenomenon, involving numerous complex interactions. Many "single target" therapies have been tried as a means to reduce the occurrence or severity of restenosis, unsuccessfully. The extent of neointimal hyperplasia and cellular proliferation in animal models of vascular injury and repair is associated with the number of adherent and infiltrating monocytes. (page 6, line 24, to page 7, line 1) As described by appellants, inhibition of integrin-mediated leukocyte adherence or function can be used to decrease the amount of neointima formed following vascular injury. These results are particularly striking in view of the complexity of the problem and the lack of success previously achieved using compounds blocking specific sites. (page 7, lines 7-12)

As defined by the claims, leukocyte adhesion or function can be inhibited or reduced by blocking cell surface integrins: Mac-1 (CD11b/CD18, αMβ2), LFA-1 (CD11a/CD18, αLβ2), p150,95 (CD11c/CD18, αXβ2) and CD11d/CD18, or their ligands. Ligands for Mac-1 include, among others, ICAM-1, fibrin(ogen), C3bi, and factor X. Ligands for LFA-1 include ICAM-1, ICAM-2, and ICAM-3. Ligands for p150,95 include fibrin(ogen) and C3bi. Exemplary

compounds for inhibiting or reducing leukocyte adhesion or function include antibodies and antibody fragments that are immunoreactive with these integrins or their ligands and which inhibit or reduce the binding of integrins or their ligands to vascular cells (claims 8 and 10); molecules which inhibit or reduce the expression of the integrins or their ligands, including nucleic acid regulators such as antisense oligonucleotides, ribozymes and external guide sequences for RNAase P, molecules involved in triplex formation, aptamers, peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells such as peptides and peptidomimetics that block the leukocyte integrin Mac-1 (claim 8 prior to amendment). The compounds can be administered systemically or administered directly to the site of vascular injury, most preferably prior to and after injury. (page 4, line 6-page 5, line 5).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-6, 8, 11 and 12 are non-enabled under 35 U.S.C. § 112, first paragraph;

(2) whether claims 1-6, 8, and 10-12 are disclosed under 35 U.S.C. § 102(e) by U.S. Patent No. 5,770,198 to Coller, et al.;

(3) whether claims 1-6, 8 and 10 are disclosed under 35 U.S.C. §102(e) by Simon, et al., Circulation 92(8 Suppl), 1-110 (1995); and

(4) whether claims 1-6, 8 and 10-12 are obvious under 35 U.S.C. § 103 over Ricevuit, et al., Atherosclerosis 91, 1-14 (1991) and/or Albelda, et al., FASEB J. 8:504-512 (1994), and/or U.S.

Patent No. 5,770,198 to Coller,et al. or Simon, et al., Circulation (1995), in view of unidentified art for administering pharmaceutical compositions and Neumann, et al., JACC 27, 819-824 (1996).

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims, whether amended as proposed in the accompanying amendment, or as currently amended, are drawn to patentably distinct subject matter.

Claim 1 is drawn to a method of treating a patient in need of treatment to inhibit or reduce restenosis of a blood vessel following injury to vascular tissue, by administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or educes leukocyte integerin-mediated adhesion or function.

Claims 2, 5, 6, 7, 9 and 10 define the integrins.

Claim 2 limits the integrins to those mediating adhesion to monocytes or granulocytes. Claim 5 (as well as claim 1, if amended as proposed by the accompanying amendment) limits the integrins to Mac-1, LFA-1, p150,95, and CD11d/CD18.

Claims 6 and 7 limit the integrin further to Mac-1 and specific Mac-1 ligands. Claim 10 is specific to antibodies to Mac-1.

Claim 9 limits the integrin to LFA-1.

Claims 3, 11 and 12, are specific to the patients to be treated, and treatment regimes,

specifically defining the patients as those undergoing angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, and transplantation (claim 3); and the time of administration as prior to vascular intervention (claim 11) or prior to and after vascular intervention until healing has occurred (claim 12).

Claim 4 is specific to the type of pharmaceutically acceptable carrier in which the active compound is administered.

Claim 8 (prior to further amendment) defines the active compound as an antibody or antibody fragment, peptides and peptidomimetics, and compounds preventing expression of the integrins. If the accompanying amendment is entered, claim 8 limits the compounds to antibodies and antibody fragments.

Since the claims are drawn to different subject matter, some of which does not raise issues under §112, such as claim 10, and others which contain limitations not disclosed at all by the prior art, such as claims 3 and 11, and other represent different combinations of elements in the art, the claims must be separately assessed for patentability.

(8) ARGUMENTS

(i) The Invention

The present invention is the discovery that a single compound can be used to prevent or inhibit restenosis. Restenosis is a very complicated disorder, known to have multiple causes and factors that can elicit or aggravate development of the disorder. Restenosis frequently develops following angioplasty, surgery and other vascular intervention. It is characterized as an

accelerated arteriopathy characterized by rapid growth of cells into the lumen within a short period of time which is severe enough to jeopardize the blood flow to distal organs.

Restenosis is accompanied by the loss of normal endothelial function. The arterial endothelium serves as a transport barrier, a biochemical filter and as a regulator of many vascular phenomena. The most potent vasodilators, thromboresistant compounds and inhibitors of smooth muscle cell proliferation, are endothelial derived. Vascular smooth muscle cell accumulation within the intima ceases with restoration of the endothelium (Schwartz et al., *Am. J. Pathol.*, *81*: 15-42 (1975); Fishman et al., *Lab. Invest.*, *32*: 339-51 (1975)) and regression of intimal hyperplasia is maximized where endothelial restoration is maximized (Bjornsson et al., *Proc. Natl. Acad. Sci. USA*, *88*: 8651-8655 (1991)). Confluent, and not exponentially growing, endothelial cells produce a series of compounds that are the most potent vasodilators, inhibitors of spasm, and inhibitors of smooth muscle cell proliferation. Heparan sulfate proteoglycan produced by the endothelial cells has multitudinous effects on the smooth muscle cells including interfering with binding of heparin-binding growth factors (Nugent et al., *Circulation Research*, *73*: 1051-1060 (1993), which are known to stimulate vascular smooth muscle cell growth (Nugent et al., *Circulation Research*, *73*: 1051-1060 (1993); Castellot et al., *J. Cell Biol.*, *90*: 372-9 (1981)). It appears, therefore, that restoring the endothelial monolayer of a blood vessel restores the agents or compounds responsible for biochemical control of vascular cell proliferation.

Other efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds.

Certain drugs, such as heparin, are especially effective inhibitors of vascular smooth muscle cell proliferation in tissue culture and animal models of arterial diseases precisely because they mimic the activity of natural endothelial-derived compounds like heparan sulfate proteoglycan, Edelman, E.R. & Karnovskv, M.J. *Circ.* 89: 770-776 (1994). However, despite cell culture and small animal data supporting the regulatory role of heparin-like compounds, exogenous heparin preparations have shown no benefit in human trials. For example, when patients were randomized to heparin or dextrose infusion over the first 18 to 24 hours post angioplasty, 41.2% of the heparinized patients and only 36.7% of the dextrose infusion patients had evidence for restenosis (Ellis et al., *Am. Heart. J., 117*: 777-782 (1989)). Moreover, bleeding complications were twice as frequent in the heparinized group. In another trial, angioplasty patients injected subcutaneously with heparin at 10,000 IU/day had 2.5 fold more restenosis and significantly more ischemic complications than patients treated in the standard fashion (Lehmann et al., *J. Am. Coll. Cardiol., 17*: 181A (abstract) (1991)). Non-heparin endothelial compounds such as nitric oxide and the prostaglandins are potent regulators of a range of biologic effects involving smooth muscle cells. Inhibitors of these compounds have been shown to control intimal hyperplasia following experimental vascular injury (Cooke et al., *Curr. Opin. Cardiol., 7*: 799-804 (1992); Moncada et al., *N. Engl. J. Med., 329*: 2002-2012 (1993); McNamara, et al., *Biochem. Biophys. Res. Comm., 193*: 291-296 (1993)). This is indicative that the vascular endothelium is a powerful regulator of the blood vessel wall, not because of the production and secretion of one compound alone, but because of its presence as an intact unit.

Accordingly, one skilled in the art would not expect a single compound to be effective in

limiting or preventing restenosis. Therefore the results obtained by appellants showing that a single class of compound, compounds blocking binding and activation of certain integrins, could effectively limit restenosis were completely unexpected. Importantly, it is not administration of a single compound, but class of compounds, that achieves this effect. These compounds inhibit or reduce leukocyte adhesion or function by interference with integrin-mediated binding. Leukocyte adhesion and function can be inhibited or reduced by blocking cell surface integrins, such as the leukocyte integrin Mac-1 (CD11b/CD18, αMβ2), LFA-1 (CD11a/CD18, αLβ2), p150,95 (CD11c/CD18, αXβ2) and CD11d/CD18, or their ligands. Ligands for Mac-1 include, among others, ICAM-1, fibrin(ogen) C3bi, and factor X. Ligands for LFA-1 include ICAM-1, ICAM-2, and ICAM-3. Ligands for p150,95 include fibrin(ogen) and C36. Mac-1, also known as CD11b/CD18, CR3, and αm/β2, is a leukocyte adhesion molecule found on monocytes, neutrophils, and natural killer lymphocytes. It binds heterogeneous ligands including, among others, fibrin(ogen), factor X, intercellular adhesion molecule-1 (ICAM-1), C3bi, and high-molecular-weight-kininogen. Suitable compounds include antibodies and antibody fragments that are immunoreactive with integrins or their ligands and which inhibit or reduce the binding of integrins or their ligands to vascular cells; molecules which inhibit or reduce the expression of integrins or their ligands, including nucleic acid regulators such as antisense oligonucleotides, ribozymes and external guide sequences for RNAase P, molecules involved in triplex formation, aptamers, and peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells.

(ii) Rejections Under 35 U.S.C. § 112, first pararaph

Claims 1-6, 8, 11 and 12 were rejected under 35 U.S.C. §112 as non-enabled, for anything other than anti-Mac1 antibodies, on the basis that the field is unpredictable and the specification lacks "working examples providing evidence which is reasonably predictive for the breadth of compounds which specifically inhibits or reduces leukocyte-integrin-mediated adhesion."

a. The Legal Requirements

35 U.S.C. §112 requires that the specification be enabling to a person skilled in the art. *See Rengo Co. Ltd. v. Molins Mach. Col.*, 657 F.2d 535, 549 (3d Cir. 1980) (every description will rely to some extent on the reader's knowledge of the terms, concepts, and depictions it embodies). The person skilled in the art is presumed to know all the art which is generally and reasonably available and has the knowledge of where to search out information. *In re Howarth*, 654 F.2d 103, 106 (CCPA 1981). The sufficiency of the specification on how to make and use the invention must be accepted unless the Patent Office provides adequate reason to doubt the accuracy of the disclosure. If the Patent Office doubts the sufficiency, then the burden shifts to the applicant to demonstrate the enablement of the disclosure by suitable evidence. Additional evidence, such as additional exemplary data and literature support, is available to substantiate any assertions that the enablement is in fact commensurate with the scope of protection sought and to respond to any demands based thereon for proof. *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Ex parte Obukowicz*, 27 USPQ2d 1063, 1066-67 (Bd. Pat. App. & Int'f 1992).

The test under 37 C.F.R. §112 is clear - the specification must be enabling to those

skilled in the art **at the time the application is filed**, without undue experimentation.

> The determination of what constitutes undue experimentation in a given case requires application of standard of reasonableness, having due regard for nature of invention and state of the art. *Ansul Co. v. Uniroyal, Inc.* supra. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable determination of how to practice desired embodiment of invention claimed. *In re Rainer*, 52 CCPA 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re Colianni, supra.
>
> *Ex parte Jackson*, 217 USPQ 804 at 807 (Bd. App. 1982).

See also *In re Wands*, 8 USPQ 1400 at 1406-1407 (Fed. Cir.), stating that it does not constitute undue experimentation even when screening of large numbers is required, if there is a relatively low percentage of positives. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff. *In re Wands* at 1407. Quoting from *Utter v. Hiraga*, 845F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988), "A specification may, within the meaning of 35 U.S.C. §112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses". Quoting from *in re Robins*, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970), "[R]epresentative samples are not required by the statute and are not an end in themselves".

The standard for making a rejection based on 35 U.S.C. § 112, first paragraph is articulated

in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (see also MPEP § 2164.01 and 2164.04). Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements (*In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)). Appellants assert that this burden has not been met.

b. The Application contains supporting data and Additional data has been provided

Data has been submitted in the application and subsequently showing the efficacy of one of these inhibitors, antibodies to Mac-1. See the examples at pages 22-23 of the application as filed, using an antibody to Mac-1 to inhibit restenosis following vascular injury. An abstract published in Circulation, Supp. 1, vol. 100, no. 18 November 2, 1999, number 1742 (attached as Exhibit 1), has also been submitted demonstrating that an equivalent effect can be obtained with a peptide inhibitor.

This is in addition to the lengthy discussion in the application as originally filed which defines the integrins and ligands (page 7, lines 13-25; page 8, line 7 to page 9, line 10; page 9, line 22-page 10, line 11); the classes of compounds, including antibodies (page 9, lines 11-22; page 10, line 10-page 11, line 19); peptides and peptidomimetics (page 11, line 20, to page 13, line 19); methods for screening for compounds and generation of synthetic compounds randomly and by computer aided design (page 13, line 20 to page 16, line 15), and nucleic acid molecules (page 16, line 16, to page 19, last line). Carrier materials are dscribed on page 20. Methods for administration are detailed at page 20, line 22, to page 22, line 2.

c. The Examiner has provided only allegations; not support for his rejections

No proper *prima facie* case for lack of enablement has been established. The Examiner has provided no evidence or convincing argument that the claimed method cannot be used for the *in vivo* purposes described in the specification. Rather, the Examiner has merely expressed the opinion that the claimed method is unpredictable. This clearly does not meet the standard to establish a *prima facie* case of lack of enablement.

No support for the lack of enablement is found in the office action mailed August 16, 1999, neither comments nor literature in support. In the previous office action mailed November 23, 1998, the examiner argued that the animal model studies in general relating to restenosis have not correlated well with clinical trial results in human patients, and that this in combination with the breadth of the claims to any compounds which would inhibit or reduce leukocyte-integrin-mediated adhesion, would mean that undue experimentation would be required to practice the claimed method. For some reason the examiner discusses the need for *in vivo* data to demonstrate that a therapy will be effective, but ignores the fact that the examples in the application as originally filed are in fact *in vivo* (although a rabbit rather than a human). There is also discussion about the fact that it takes years of development to prove a clinical treatment. The truth of this is indisputable but not relevant: the fact is that the appellants have provided *in vivo* evidence in their application showing that an antibody to at least one of the claimed integrins was effective in an animal model and in combination with independent third parties have provided evidence that another completely different kind of molecule, a peptide, derived from the integrin ligand glycolipid-anchored urokinase receptor, was also effective. The examiner has not responded to the latter evidence.

1. Animal Models are Predictive of Efficacy

The rejection is initially based on the proposition that the animal models, specifically the rat and rabbit animal models used by applicants, do not correlate well with *in vivo* clinical trial results. Enclosed in response were three papers and abstracts of two others (copies of which are attached as Exhibit 2). The abstract of Coats, et al., "Remodeling and restenosis: insights from animal studies" Semin. Interv. Cardiol. 2(3), 153-158 (1997), notes that animal studies in remodeling and its contribution to restenosis have been critical, and correlated with human studies. Farb., et al., "Pathology and Chronic Coronary Stenting in Humans," Circulation, 99:44-52 (1999), paper notes at page 51, col. 2, that "These data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting early after implantation (with a relatively longer duration of healing in humans)." The authors then note that there is a difference in the type of vascular injury in normal arteries of animals as compared to the response in human atherosclerotic arteries. (This may be one reason why there has been variable correlation with some reported models). Komatsu, et al., "Neointimal Tissue Response at Sites of Coronary Stenting in Humans" Circulation 98, 224-233 (1998), reports that animal models are generally predictive (page 230), with dogs being an exception (page 232). Kearney, et al., "Histopathology of In-Stent Restenosis in Patients with Peripheral Artery Disease", Circulation, 95:1998-2002 (1997) correlates results in humans obtained at autopsy with animal studies, beginning at the bottom of page 1999, col. 2. The abstract of Folts, et al., J. Am. Coll. Cardio. 33(2), 295-303 (1999), notes that an animal model, the cyclic flow model of coronary thrombosis, has been useful in predicting which agents are likely to be of benefit in

clinical trials.

In summary, the literature supports the use of animal models as predictive of efficacy.

2. Data demonstrates Efficacy of Inhibiting Integrin-mediated Inhibition

Example 2, beginning on page 22 of the application, shows administration of an antibody to rabbits after arterial injury. The data demonstrated that there was a reduction in neointimal area after deep injury of nearly 40% relative to controls. This data alone indicates that the active agent can be effectively delivered. No adverse effects were noted.

Also provided to the examiner (and enclosed in Exhibit 3) was an article by the authors and others which was submitted to the J. Clin. Invest. entitled "Decreased neointimal formation in Mac-1 (-/-) mice reveals a role for inflammation in vascular repair after angioplasty. (published by Simon, et al., J. clin. Invest. 105(3), 293-300 (February 2000)). This paper describes the role of inflammation in mechanical arterial injury, in particular Mac-1, which when absent results in significantly less intimal proliferation and thickening after injury.

3. There are numerous protein therapies

The relevance of the comments regarding potential degradation of compound, etc. at pages 3-4 of the office action is not clear. Many pharmaceutical proteins and numerous antibodies are administered to patients as therapeutics, absent side effects, and without loss of function. For example, as shown by the abstract by Topol, et al., "Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa

Inhibition for Prevention of Ischemic Complication" JAMA 278(6):479-484 (1997). (Exhibit 4)

Summary

In summary, the examiner has provided mere assumption, not specific support, for alleging that the application is non-enabling. Appellants have responded by pointing to the specific support in the application as well as to supporting data. No rebuttal has been made by the examiner. Therefore the claims should be determined to be enabled by the Board of Appeals.

(iii) Rejections Under 35 U.S.C. § 102

Claims 1-6, 8 and 10 were rejected under 35 U.S.C. §102(e) as disclosed by Simon, et al., Circulation 92(8 Suppl), 1-110 (1995) or U.S. Patent No. 5,770,198 to Coller, et al..

The claims are drawn to "an effective amount of a compound specifically inhibiting or reducing leukocyte adhesion or function mediated by an integrin (selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18" as defined by claim 5 or proposed amended claim 1) to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

a. Simon, et al. (Circulation)

Simon, et al., (Circulation) reports on studies using an antibody fragment c7E3 immunoreactive with platelet glycoprotein IIb/IIa. The abstract reports that the antibody was effective at reducing **"ischemic complications"** six months after coronary angioplasty and clinical restenosis. The abstract also reports that the antibody is cross-reactive with Mac-1.

b. Coller, et al.

Coller et al., describes the 7E3 antibody which is discussed by Simon, et al.,

(Circulation). The patent reports that the antibody is specific for glycoprotein IIb/IIIa and can be used as an antithrombotic agent. There is no disclosure of the use of the antibody to inhibit or prevent restenosis.

c. 7E3 Antibody does not inhibit Restenosis.

The 7E3 antibody is known to inhibit integrin binding in cell culture, and be very effective in treating thrombotic conditions. However, treatment of thrombotic complications (i.e., ischemia and ischemia-reperfusion injury) is not the same as, nor predictive of, treatment of patients to prevent or reduce restenosis. The abstract does not report treatment of patients, the dosages, the times of administration nor indeed is that the focus of the abstract. The abstract reports *in vitro* studies that identify the activity of the antibody as cross-reactive with Mac-1 as well as platelet glycoprotein IIb/IIa. The patent describes treatment of a different class of patients, at different administration times and dosages.

Thrombolysis causes injury due to a disruption in blood flow, followed by reperfusion, where the endothelium is intact.

Restenosis is injury arising when there is disruption in the endothelium while the blood flow remains continuous. Restenosis involves recruitment of platelets and leukocytes. As shown by abstract, Mickelson, et al., "Chimeric 7E3 Fab (ReoPro) decreases detectable CD11b on neutrophils from patients undergoing coronary angioplasty", J. Am. Coll. Cardiol. 33(1):97-106 (1999), (Exhibit 5), this antibody decreases detectable CD11b on neutrophils but does not bind to neutrophils nor inhibit adhesion, two of the major factors involved in restenosis. See also Deitch, et al., "Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and

intra-arterial stenting in atherosclerotic nonhuman primates", Arterioscler. Thromb. Vasc. Biol. 18(11):1730-7 (1998 Nov. As further shown by the paper, The Eraser Investigators, "Acute Platelet Inhibition with Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation 100:799-806 (1999) (Exhibit 5), this antibody did not inhibit restenosis.

This evidence demonstrates that this antibody ("Reopro") does not affect restenosis and that this is not an inherent property of the antibody. Therefore neither Simon, et al., nor Coller, et al. disclose the claimed subject matter.

(iv) Rejections Under 35 U.S.C. § 103

Claims 1-6, 8 and 10-12 were rejected as obvious under 35 U.S.C. § 103 over Ricevuit, et al., Atherosclerosis 91, 1-14 (1991) and/or Albelda, et al., FASEB J. 8:504-512 (1994), and/or U.S. Patent No. 5,770,198 to Coller,et al. or Simon, et al., Circulation (1995), in view of unidentified art for administering pharmaceutical compositions and Neumann, et al., JACC 27, 819-824 (1996).

a. The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

b. *Simon and Coller*

Simon and Coller are discussed above. They do not describe an antibody that inhibits restenosis.

c. *Ricevuti*

Ricevuti, et al., discusses the role of granulocytes in endothelial injury, as examined by reacting a monoclonal antibody to CD11b/CD18. This paper relates to ischemia and ischemia-reperfusion; not restenosis. As discussed above, and as clearly established by the ERASER study, a copy of which is enclosed (Exhibit ~~6~~ 5), these are distinct disorders, with very different mechanisms, patient populations, outcomes, and a compound effective to treat one cannot be predicted to be efficacious in treating the other.

d. *Albelda, et al.*

Albelda, also discusses the role of antibodies to CD11/CD18 integrins to endothelial

ligands such as intercellular adhesion molecule-1 (ICAM-1) involved in inflammation and, as the examiner has noted, "to inhibit neutrophil influx in almost every system to date including the heart and ischemia reperfusion". However, there is no mention of preventing restenosis. Many studies have shown binding to integrins - in fact, as extensively discussed above, the antibody cited by the Examiner binds to the integrin - but it does not stop neutrophil recruitment or adhesion, and it does not decrease restenosis.

e. *Neumann, et al.*

Neumann measured the presence of several molecules on platelets, before and after dilated coronary artery plaque. The results demonstrated that there was increased expression of the activated fibrinogen receptor LIBS1 on platelets as well as Mac-1 (CD11b) and L-selectin (CD62L) on neutrophils, indicating generally that there was neutrophil and platelet activation at the injured artery. There is no cause and effect here. It is just as likely these are markers arising from injury as causative agents. Therefore these results are not predictive that the claimed compounds can be used to treat restenosis.

f. *Summary*

The art cited by the examiner relates to reperfusion and ischemia (Albelda and Ricevuti), not restenosis; platelet and neutrophil activation generally following arterial activation (Neumann); and an antibody which may be cross-reactive with Mac-1 *in vitro* but is not cross-reactive *in vivo,* nor does it demonstrate any clinical effectiveness against restenosis.

Results obtained relative to ischemia and reperfusion are not predictive of results obtained in the treatment of restenosis. The mechanisms are different, the treatments are

different, the outcomes are different. Even the markers associated with restenosis are different from those associated with reperfusion. No art has been cited which would indicate that there is any teaching that ischemia is predictive of restenosis. Applicant has provided irrefutable evidence in fact that the prior art compound described as efficacious for treatment of ischemic disorders is NOT effective in treating restenosis. Therefore, compounds which relate to the treatment of ischemia and reperfusion are not encompassed by the claims. No compounds which "specifically inhibit or reduce leukocyte CD11/CD18 integrin-mediated adhesion or function", as required by claim 1, have been associated with treatment or prevention of restenosis, as required by the claims, much less is there any teaching in the cited art that would lead one skilled in the art to use compounds known for the treatment of ischemia for the treatment of restenosis, even less so with any expectation of success. Therefore the claimed subject matter cannot be obvious from the cited art.

(9) SUMMARY

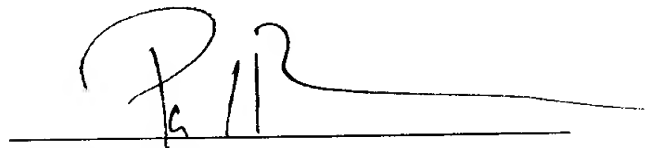
Claims 1-12 are enabled by the specification. No evidence has been provided by the examiner to support the rejection, and appellants have provided a detailed description in the application and in supporting data in the application and as subsequently published in support of the breadth of their claims.

Claims 1-12 define a method of preventing or inhibiting restenosis that is neither disclosed by, nor obvious from, the prior art cited by the examiner. Coller and Simon, et al. (Circulation) do not inherently disclose the claimed method. The other art cited by the examiner fails to make up for the deficiencies of Coller, et al. and Simon, et al.

(10) CONCLUSION

Claims 1-12 should be determined to be patentably under 35 U.S.C. §112, 102 and 103.

Respectfully submitted,



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Appendix I: Claims as pending

1. A method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte CD11d/CD18 integrin -mediated adhesion or function, wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with CD11d/CD18 integrins or their ligands and which block the interaction of the CD11d/CD18 integrins or their ligands with vascular cells; molecules which inhibit expression of the CD11d/CD18 integrins or their ligands, and peptides and peptidomimetics derived from the CD11d/CD18 integrins or their ligands which block the interaction of the CD11d/CD18 integrins or their ligands with vascular cells or tissues, in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

2. The method of claim 1 wherein the leukocytes are monocytes or granulocytes.

3. The method of claim 1 wherein the injury arises from angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs.

4. The method of claim 1 wherein the composition is in a form selected from the group consisting of solutions, gels, foams, suspensions, polymeric carriers, and liposomes.

5. The method of claim 1 wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18.

6. The method of claim 5 wherein the CD11/CD18 integrin is Mac-1.

7. The method of claim 6 wherein the ligand is selected from the group consisting of ICAM-1, fibrin(ogen), C3bi, and factor X.

8. The method of claim 1 wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with CD11/CD18 integrins or their ligands and which block the interaction of the CD11/CD18 integrins or their ligands with vascular cells; molecules which inhibit expression of the integrins or their ligands, and peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells or tissues.

9. The method of claim 5 wherein the CD11/CD18 integrin is LFA-1 and the ligand is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3.

10. The method of claim 6 wherein the compound is an antibody or antibody fragment immunoreactive with Mac-1.

11. The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

Appendix II: Claims as proposed to be amended

1. A method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin - mediated adhesion or function, wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18, wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or their ligands and which block the interaction of the integrins or their ligands with vascular cells; molecules which inhibit expression of the integrins or their ligands, and peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells or tissues, in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

2. The method of claim 1 wherein the leukocytes are monocytes or granulocytes.

3. The method of claim 1 wherein the injury arises from angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs.

4. The method of claim 1 wherein the composition is in a form selected from the group consisting of solutions, gels, foams, suspensions, polymeric carriers, and liposomes.

5. The method of claim 1 wherein the integrin is selected from the group consisting of LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18.

6. The method of claim 5 wherein the integrin is Mac-1 (CD11b/CD18).

7. The method of claim 6 wherein the ligand is selected from the group consisting of ICAM-1, fibrin(ogen), C3bi, and factor X.

8. The method of claim 1 wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or their ligands and which block the interaction of the integrins or their ligands with vascular cells.

9. The method of claim 5 wherein the integrin is LFA-1 and the ligand is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3.

10. The method of claim 6 wherein the compound is an antibody or antibody fragment immunoreactive with Mac-1 (CD11b/CD18).

11. The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

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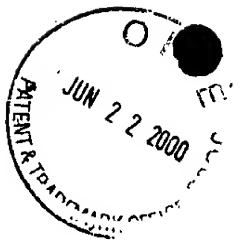

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this Appeal Brief, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: June 19, 2000

Jean Hicks